REMARKS

Claims 1, 4-8, 14, 16-20, 49, 51-57, 60-64, 98 and 100-14 are currently pending in the application. Claims 2, 9, 10, 12, 13, 21, 22, 24-48, 59 and 65-93 have been withdrawn from consideration due to the Examiner's previous restriction requirement. Claims 3, 11, 15, 23, 50, 58, 94-97, 99, 105 and 106 have been canceled in a previous reply. These claims have been withdrawn or canceled without prejudice to, or disclaimer of, the subject matter thereof. Applicants reserve the right to file divisional and continuing applications directed to the subject matter of any claim withdrawn or cancelled for any reason.

Claims 1, 14, 49, 57 and 98 have been amended in the present reply. It is submitted that no new matter has been introduced by these amendments, and entry of the same is respectfully requested. By these amendments, Applicants do not acquiesce to the propriety of any of the Examiner's prior rejections and does not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 USPQ.2d 1865 (US 1997).

I. Claim Rejections under 35 U.S.C. § 112

Claims 1, 4-8, 14, 16-20, 49, 51-57, 60-64, 98 and 100-104 stand rejected under 35 U.S.C. § 112 as allegedly not enabled by the specification. February 6, 2008 Office Action ("OA"), page 3. According to the Examiner, the specification "does not reasonably provide enablement for all phosphodiesterase inhibitors" and "does not enable any person skilled in the art to which it pertains ... to practice the invention commensurate in scope with these claims ... without undue experimentation." *Id.* Applicants respectfully traverse.

When making a rejection on the ground of alleged lack of enablement, the USPTO has the "initial burden of setting forth a reasonable explanation as to why [he/she] believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *Id.; see also In re Marzocchi*, 439 F.2d 220 (C.C.P.A. 1971).

In maintaining the present rejections under 35 U.S.C. § 112 the Examiner applied the *In re Wand* factors (8 U.S.P.Q. 1400, 1404 (Fed. Cir. 1988)) as described

below. Applicants' responses regarding the Examiner's application of each factor is provided immediately following the Examiner's application.

A. Wands Factors

1. Nature of the Invention

Examiner's Application: "The rejected claims are drawn to an invention which pertains to a method of increasing performance gain during treatment of a cognitive deficit associated with a central nervous system disorder by administering any or all phosphodiesterase inhibitors." OA, page 3.

Applicants' Response: Applicants agree that the present invention, *inter alia*, pertains to that invention.

2. State of the Prior Art

Examiner's Application: "The state of the art regarding phosphodiesterase inhibitors is relatively high, however, the state of the art regarding a method of increasing performance gain during treatment of a cognitive deficit associated with a central nervous system disorder by administering any or all phosphodiesterase inhibitors is low." OA, page 4.

Applicants' Response: Applicants respectfully submit that the present specification, when read and understood by one of ordinary skill in the art, teaches the claimed method such that that "one skilled in the art would be able to make and use the claimed invention using the application as a guide." M.P.E.P. § 2164.05 (*citing In re Brandstadter*, 484 F.2d 1395, 1406-07, 179 USPQ 286, 294 (C.C.P.A. 1973)). For example, the present specification teaches that:

> As described herein, [Augmented Cognitive Training (ACT)] comprises two indivisible parts: (1) a specific training protocol for each brain (cognitive) function and (2) administration of cyclic AMP response element binding protein (CREB) pathway-enhancing drugs. ¶ 7. ...
>
> Cognitive training protocols (e.g., physical therapy, bio-feedback methods) are employed in rehabilitating stroke patients (stroke rehabilitation), particularly rehabilitating impaired or lost sensory-motor function(s). Administration of a CREB pathway-enhancing drug in conjunction with cognitive training reduces the time and/or number of training sessions required to yield a gain in performance in these patients. Faster and more efficient recovery of lost cognitive function(s) is expected as a result. ¶ 10. ...
>
> Cognitive training protocols are employed for repeated stimulation of neuronal activity or a pattern of neuronal activity underlying (a) specific

neuronal circuit(s) in individuals. Administration of a CREB pathway-enhancing drug in conjunction with cognitive training reduces the time and/or number of training sessions and/or underlying pattern of neuronal activity required to induce CREB-dependent long-term structure/function (i.e., long-lasting) change among synaptic connections of the neuronal circuit. ¶ 14.

As a result of the present invention, methods of enhancing a specific aspect of cognitive performance in an animal (particularly a human or other mammal or vertebrate) in need thereof are provided herein comprising (a) administering to the animal an augmenting agent which enhances CREB pathway function; and (b) training the animal under conditions sufficient to produce an improvement in performance of a cognitive task of interest by the animal. "Augmenting agents" are also referred to herein as "CREB pathway-enhancing drugs". ¶ 15.

Methods are provided herein for treating a cognitive deficit associated with a central nervous system (CNS) disorder or condition in an animal in need of said treatment comprising (a) administering to the animal an augmenting agent which enhances CREB pathway function; and (b) training the animal under conditions sufficient to produce an improvement in performance of a particular cognitive task by the animal. CNS disorders and conditions include age-associated memory impairment, neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease (chorea), other senile dementia), psychiatric diseases (e.g., depression, schizophrenia, autism, attention deficit disorder), trauma dependent loss of function (e.g., cerebrovascular diseases (e.g., stroke, ischemia), brain tumor, head or brain injury), genetic defects (e.g., Rubinstein-Taybi syndrome, down syndrome) and learning disabilities. ¶ 16. ...

The present invention relates to a novel methodology, also referred to herein as augmented cognitive training (ACT), which can (1) rehabilitate various forms of cognitive dysfunction or (2) enhance normal cognitive performance. ACT acts via a general molecular mechanism of synaptic plasticity, which apparently converts the biochemical effect of a newly acquired experience into a long-lasting structural change of the synapse. ACT can be applied for any aspect of brain function that shows a lasting performance gain after cognitive training. Accordingly, ACT can be used in rehabilitating an animal with any form of cognitive dysfunction or in enhancing or improving any aspect of normal cognitive performance in an animal. ¶ 28. ...

ACT comprises a specific training protocol for each brain function and a general administration of CREB pathway-enhancing drugs. The training protocol (cognitive training) induces neuronal activity in specific brain regions and produces improved performance of a specific brain (cognitive) function. CREB pathway-enhancing drugs, also referred to herein as augmenting agents, enhance CREB pathway function, which is

required to consolidate newly acquired information into LTM. By "enhance CREB pathway function" is meant the ability to enhance or improve CREB-dependent gene expression. CREB-dependent gene expression can be enhanced or improved by increasing endogenous CREB production, for example by directly or indirectly stimulating the endogenous gene to produce increased amounts of CREB, or by increasing functional (biologically active) CREB. See, e.g., U.S. Pat. No. 5,929,223; U.S. Pat. No. 6,051,559; and International Publication No. WO9611270 (published Apr. 18, 1996), which references are incorporated herein in their entirety by reference. Administration of CREB pathway-enhancing drugs decreases the training needed to yield a performance gain relative to that yielded with training alone. In particular, ACT can enhance cognitive training by reducing the number of training sessions required to yield a performance gain relative to that yielded with cognitive training alone or by requiring shorter or no rest intervals between training sessions to yield a performance gain. In this manner, ACT can improve the efficiency of cognitive training techniques, thereby yielding significant economic benefit. By "performance gain" is meant an improvement in an aspect of cognitive performance. ¶ 30.

The invention provides methods for enhancing a specific aspect of cognitive performance in an animal (particularly in a human or other mammal or vertebrate) in need thereof comprising (a) administering to the animal an augmenting agent which enhances CREB pathway function; and (b) training the animal under conditions sufficient to produce an improvement in performance of a particular cognitive task by the animal. ¶ 31.

Training can comprise one or multiple training sessions and is training appropriate to produce an improvement in performance of the cognitive task of interest. For example, if an improvement in language acquisition is desired, training would focus on language acquisition. If an improvement in ability to learn to play a musical instrument is desired, training would focus on learning to play the musical instrument. If an improvement in a particular motor skill is desired, training would focus on acquisition of the particular motor skill. The specific cognitive task of interest is matched with appropriate training. ¶ 32. ...

By "multiple training sessions" is meant two or more training sessions. The augmenting agent can be administered before, during or after one or more of the training sessions. In a particular embodiment, the augmenting agent is administered before and during each training session. Treatment with augmenting agent in connection with each training session is also referred to as the "augmenting treatment". By "training" is meant cognitive training. ¶ 34.

Cognitive training protocols are known and readily available in the art. See for example, Karni, A. and Sagi, D., "Where practice makes perfect

in text discrimination: evidence for primary visual cortex plasticity", Proc. Natl. Acad. Sci. USA, 88:4966-4970 (1991); Karni, A. and Sagi, D., "The time course of learning a visual skill", Nature, 365:250-252 (1993); Kramer, A. F. et al., "Task coordination and aging: explorations of executive control processes in the task switching paradigm", Acta Psychol. (Amst.), 101:339-378 (1999); Kramer, A. F. et al., "Training for executive control: Task coordination strategies and aging", In Aging and Skilled Performance: Advances In Theory and Applications, W. Rogers et al., eds. (Hillsdale, N.J.: Erlbaum) (1999); Rider, R. A. and Abdulahad, D. T., "Effects of massed versus distributed practice on gross and fine motor proficiency of educable mentally handicapped adolescents", Percept. Mot. Skills, 73:219-224 (1991); Willis, S. L. and Schaie, K. W., "Training the elderly on the ability factors of spatial orientation and inductive reasoning", Psychol. Aging, 1:239-247 (1986); Willis, S. L. and Nesselroade, C. S., "Long-term effects of fluid ability training in old-old age", Develop. Psychol., 26:905-910 (1990); Wek, S. R. and Husak, W. S., "Distributed and massed practice effects on motor performance and learning of autistic children", Percept. Mot. Skills, 68:107-113 (1989); Verhaehen, P. et al., "Improving memory performance in the aged through mnemonic training: a meta-analytic study", Psychol. Aging, 7:242-251 (1992); Verhaeghen, P. and Salthouse, T. A., "Meta-analyses of age-cognition relations in adulthood: estimates of linear and nonlinear age effects and structural models", Psychol. Bull., 122:231-249 (1997); Dean, C. M. et al., "Task-related circuit training improves performance of locomotor tasks in chronic stroke: a randomized, controlled pilot trial", Arch. Phys. Med. Rehabil., 81:409-417 (2000); Greener, J. et al., "Speech and language therapy for aphasia following stroke", Cochrane Database Syst. Rev., CD000425 (2000); Hummelsheim, H. and Eickhof, C., "Repetitive sensorimotor training for arm and hand in a patient with locked-in syndrome", Scand. J. Rehabil. Med., 31:250-256 (1999); Johansson, B. B., "Brain plasticity and stroke rehabilitation. The Willis lecture", Stroke, 31:223-230 (2000); Ko Ko, C., "Effectiveness of rehabilitation for multiple sclerosis", Clin. Rehabil., 13 (Suppl. 1):33-41 (1999); Lange, G. et al., "Organizational strategy influence on visual memory performance after stroke: cortical/subcortical and left/right hemisphere contrasts", Arch. Phys. Med. Rehabil., 81:89-94 (2000); Liepert, J. et al., "Treatment-induced cortical reorganization after stroke in humans", Stroke, 31:1210-1216 (2000); Lotery, A. J. et al., "Correctable visual impairment in stroke rehabilitation patients", Age Ageing, 29:221-222 (2000); Majid, M. J. et al., "Cognitive rehabilitation for memory deficits following stroke" (Cochrane review), Cochrane Database Syst. Rev., CD002293 (2000); Merzenich, M. et al., "Cortical plasticity underlying perceptual, motor, and cognitive skill development: implications for neurorehabilitation", Cold Spring Harb. Symp. Quant. Biol., 61:1-8 (1996); Merzenich, M. M. et al., "Temporal processing deficits of language-learning impaired children ameliorated by training", Science, 271:77-81 (1996); Murphy, E., "Stroke rehabilitation", J. R. Coll. Physicians Lond., 33:466-468 (1999); Nagarajan, S. S. et al., "Speech modifications algorithms used for training language learning-

> impaired children", IEEE Trans. Rehabil. Eng., 6:257-268. (1998); Oddone, E. et al., "Quality Enhancement Research Initiative in stroke: prevention, treatment, and rehabilitation", Med. Care 38:192-1104 (2000); Rice-Oxley, M. and Turner-Stokes, L., "Effectiveness of brain injury rehabilitation", Clin. Rehabil., 13(Suppl 1):7-24 (1999); Tallal, P. et al., "Language learning impairments: integrating basic science, technology, and remediation", Exp. Brain Res., 123:210-219 (1998); Tallal, P. et al., "Language comprehension in language-learning impaired children improved with acoustically modified speech", Science, 271:81-84 (1996), which references are incorporated herein in their entirety by reference. ¶ 35.

3. Breadth of Claims

Examiner's Application: "The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass every known inhibitor of phosphodiesterase." OA, page 4. In maintaining the outstanding rejection of claims 1, 4-8, 14, 16-20, 49, 51-57, 60-64, 98 and 100-104 under 35 U.S.C. § 112, the Examiner also states that "no further data points commensurate with the scope of the claims ... are disclosed in the ... [previously submitted] declaration." OA, page 6.

Applicants' Response: The present application provides the broad and far-reaching teaching that:

> As described herein, ACT comprises two indivisible parts: (1) a specific training protocol for each brain (cognitive) function and (2) administration of cyclic AMP response element binding protein (CREB) pathway-enhancing drugs. This combination can augment cognitive training by reducing the number of training sessions required to yield a performance gain relative to that obtained with cognitive training alone or by requiring shorter or no rest intervals between training sessions to yield a performance gain. This combination can also augment cognitive training by reducing the duration and/or number of training sessions required for the induction in a specific neuronal circuit(s) of a pattern of neuronal activity or by reducing the duration and/or number of training sessions or underlying pattern of neuronal activity required to induce CREB-dependent long-term structural/function (i.e., long-lasting) change among synaptic connections of the neuronal circuit. In this manner, ACT can improve the efficiency of existing cognitive training protocols, thereby yielding significant economic benefit. ¶ 7.

The specification also teaches that:

> [A]ugmenting agents can be ... inhibitors of the phosphodiesterases responsible for cAMP breakdown... ¶ 55.

In the context of this broad teaching, Applicants respectfully remind the Examiner that:

> The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does granting of specific claims on more specific inventions. It is neither contemplated by the public purpose of the patent laws nor required by the statute that an inventor shall be forced to accept claims narrower than his invention in order to secure allowance of his patent.

Application of Sus, 306 F.2d 494 (C.C.P.A. 1962). Here, the specification teaches that phosphodiesterase inhibitors can be used in accordance with the methods of the present invention. This teaching reflects the appropriate breadth of the claims.

Additionally, Applicants respectfully disagree with the Examiner's statement that "no further data points commensurate with the scope of the claims ... are disclosed in the ... declaration." (OA, page 6) and direct the Examiner's attention to Exhibit B of Timothy Tully's declaration submitted under 37 C.F.R. § 1.132. Particularly, and as explained in the submitted declaration at ¶ 6, the provided data shows "the efficacy of the phosphodiesterase inhibitor HT0712 in promoting rehabilitation dependent motor recovery and enhancing functional restoration within the motor cortex following cortical ischemia." Applicants respectfully submit that this data demonstrates the enablement provided by the pending specification by demonstrating that the phosphodiesterase inhibitor HT0712 increases performance gain as claimed.

Nonetheless, and solely to expedite prosecution of the pending claim set, the pending claims have been narrowed to claim the use of phosphodiesterase 4 inhibitors with the methods of the present invention. This amendment is discussed in more detail below.

4. Guidance of the Specification

Examiner's Application: "The guidance of the specification as to the method of increasing performance gain during treatment of a cognitive deficit associated with a central nervous system disorder by administering all phosphodiesterase inhibitors is lacking, with the exception of rolipram and iso-buto-metho-xanthine." OA, page 4.

Applicants' Response: The Examiner appears to improperly restrict the scope of enablement to the subject matter of the specific examples provided in the specification. This interpretation is supported by the Examiner's statement in the present office action (addressing previously made arguments by the Applicants) that

"reminded" the Applicants that the specification is "limited to only two examples of phosphodiesterase inhibitor, rolipram and iso-buto-metho-xanthine." OA, page 5.

Applicants respectfully assert that the Examiner improperly uses the fact that two examples are provided to unduly limit the scope of enablement. The case of *Application of Marzocchi* is enlightening in this regard. In *Application of Marzocchi*, it was explained that:

> It has never been contended that appellants, ..., intended only to indicate a single compound. Accepting, therefore, that the term is a generic one, its recitation must be taken as an assertion by the appellants that all of the "considerable number of compounds" that are included within the generic term would, as a class, be operative to produce the asserted enhancement of ... characteristics. The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of 35 U.S.C. § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples *or by broad terminology*, is of no importance.

439 F.2d 220 (C.C.P.A. 1971) (emphasis added); *see also* MPEP § 2164.08 ("[H]ow a teaching is set forth, by specific examples or broad terminology, is not important."). Furthermore, in *In re Strahilevitz*, the Examiner's position that, because of the breadth of the invention, a large number of examples (50 to 100) would be required was rejected (668 F.2d 1229 (C.C.P.A. 1982)), and the Federal Circuit has cautioned that patent applicants are not required to disclose every species encompassed by their claims, even in unpredictable arts. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 13 (Fed. Cir. 1999).

Here, the specification provided two examples of known phosphodiesterase inhibitors, rolipram and iso-buto-metho-xanthine. However, the invention is drawn to the use of any phosphodiesterase inhibitor and should not be limited to the provided examples. As in *In re Application of Marzocchi*, there is no evidence that Applicants intended to limit their disclosure to the provided examples and the scope of their claims should not be limited to those embodiments that are expressly disclosed. Based on the foregoing, Applicants respectfully submit that the Examiner has erred in restricting the scope of enablement to the two provided examples of phosphodiesterase inhibitors provided in the specification. MPEP § 2164.08 ("[L]imitations and examples in the specification do not generally limit what is covered by the claims.").

5. The Predictability or Unpredictability of the Art

Examiner's Application: "The invention is directed to a method of increasing performance gain during treatment of a cognitive deficit associated with a central nervous system disorder by administering all phosphodiesterase inhibitors. It is unpredictable to know that all phosphodiesterase inhibitors will have the same function." OA, page 4.

Applicants' Response: The Declaration previously submitted by Timothy Tully under 37 C.F.R. § 1.132 addresses this concern of the Examiner by clearly establishing that the mechanism in which an augmenting agent which enhances CREB pathway function by inhibiting phosphodiesterase in combination with cognitive training would result in performance gain during treatment of a cognitive deficit associated with a central nervous system disorder. OA, page 6. This explanation serves to bolster the predictability of the claimed invention by explaining the mechanism by which the claimed class of compounds functions to produce the claimed effect.

6. The Relative Skill of those in the Art

Examiner's Application: "One of ordinary skill in the art does not know how to increase performance gain during treatment of a cognitive deficit associated with a central nervous system disorder by administering all phosphodiesterase inhibitors. On of ordinary skill in the art cannot identify all suitable phosphodiesterase inhibitors, let alone for the purpose of treating cognitive deficit associated with a central nervous system disorder." OA, page 4 (*sic*). In regard to this factor, the Examiner also states that "one of ordinary skill does not know how to identify every inhibitor of phosphodiesterases let alone apply the inhibitor in a method of increasing performance gain during treatment of a cognitive deficit associated with a central nervous system disorder without undue experimentation." OA, page 5.

Applicants' Response: It is submitted that one of ordinary skill in the art would need to determine whether a particular compound is a phosphodiesterase inhibitor if this knowledge regarding a compound was not known in the art. Note, however, that many such compounds were known at the time of the present application's priority date. See, for example, Basic Neurochemistry, Part Three, section 22, ed. Seigel *et al.*, Lippincott, Sixth Edition (1999), including, for example, Table 22-1 listing many known phosphodiesterase inhibitors. Methods for determining whether a particular compound inhibits phosphodiesterase activity were also well known in the art at the

time of the present application's priority date. For example, WO/1997/018208, entitled "Quinolone Derivatives as Type IV Phosphodiesterase Inhibitors" (submitted herewith) describes a phosphodiesterase inhibition assay. WO/1996/040636, entitled "Catechol Diethers Derivatives Useful as Pharmaceutical Agents" (submitted herewith) also describes a phosphodiesterase inhibition assay. The references Weiss, B.: Differential activation and inhibition of the multiple forms of cyclic nucleotide phosphodiesterase. Adv. Cycl. Nucl. Res. 5:195-211, 1975 and Weiss, B. and Hait, W.N.: Selective cyclic nucleotide phosphodiesterase inhibitors as potential therapeutic agents. Ann. Rev. Pharmacol. Toxicol. 17:441-477, 1977 (both submitted herewith) also show that methods of determining phosphodiesterase inhibition existed as early as the 1970s.

Moreover, a vast number of cognitive training experimental protocols in both human and animal models were known at the present application's priority date, and these experimental protocols can be used to determine performance gains during treatment of a cognitive deficit associated with a central nervous system disorder. For example, the present specification provides the following examples of appropriate experimental protocols that demonstrate the sophistication in the art:

> Cognitive training protocols are known and readily available in the art. See for example, Karni, A. and Sagi, D., "Where practice makes perfect in text discrimination: evidence for primary visual cortex plasticity", Proc. Natl. Acad. Sci. USA, 88:4966-4970 (1991); Karni, A. and Sagi, D., "The time course of learning a visual skill", Nature, 365:250-252 (1993); Kramer, A. F. et al., "Task coordination and aging: explorations of executive control processes in the task switching paradigm", Acta Psychol. (Amst.), 101:339-378 (1999); Kramer, A. F. et al., "Training for executive control: Task coordination strategies and aging", In Aging and Skilled Performance: Advances In Theory and Applications, W. Rogers et al., eds. (Hillsdale, N.J.: Erlbaum) (1999); Rider, R. A. and Abdulahad, D. T., "Effects of massed versus distributed practice on gross and fine motor proficiency of educable mentally handicapped adolescents", Percept. Mot. Skills, 73:219-224 (1991); Willis, S. L. and Schaie, K. W., "Training the elderly on the ability factors of spatial orientation and inductive reasoning", Psychol. Aging, 1:239-247 (1986); Willis, S. L. and Nesselroade, C. S., "Long-term effects of fluid ability training in old-old age", Develop. Psychol., 26:905-910 (1990); Wek, S. R. and Husak, W. S., "Distributed and massed practice effects on motor performance and learning of autistic children", Percept. Mot. Skills, 68:107-113 (1989); Verhaehen, P. et al., "Improving memory performance in the aged through mnemonic training: a meta-analytic study", Psychol. Aging, 7:242-251 (1992); Verhaeghen, P. and Salthouse, T. A., "Meta-analyses of age-cognition relations in adulthood: estimates of linear and nonlinear age effects and structural models", Psychol. Bull., 122:231-249 (1997);

> Dean, C. M. et al., "Task-related circuit training improves performance of locomotor tasks in chronic stroke: a randomized, controlled pilot trial", Arch. Phys. Med. Rehabil., 81:409-417 (2000); Greener, J. et al., "Speech and language therapy for aphasia following stroke", Cochrane Database Syst. Rev., CD000425 (2000); Hummelsheim, H. and Eickhof, C., "Repetitive sensorimotor training for arm and hand in a patient with locked-in syndrome", Scand. J. Rehabil. Med., 31:250-256 (1999); Johansson, B. B., "Brain plasticity and stroke rehabilitation. The Willis lecture", Stroke, 31:223-230 (2000); Ko Ko, C., "Effectiveness of rehabilitation for multiple sclerosis", Clin. Rehabil., 13 (Suppl. 1):33-41 (1999); Lange, G. et al., "Organizational strategy influence on visual memory performance after stroke: cortical/subcortical and left/right hemisphere contrasts", Arch. Phys. Med. Rehabil., 81:89-94 (2000); Liepert, J. et al., "Treatment-induced cortical reorganization after stroke in humans", Stroke, 31:1210-1216 (2000); Lotery, A. J. et al., "Correctable visual impairment in stroke rehabilitation patients", Age Ageing, 29:221-222 (2000); Majid, M. J. et al., "Cognitive rehabilitation for memory deficits following stroke" (Cochrane review), Cochrane Database Syst. Rev., CD002293 (2000); Merzenich, M. et al., "Cortical plasticity underlying perceptual, motor, and cognitive skill development: implications for neurorehabilitation", Cold Spring Harb. Symp. Quant. Biol., 61:1-8 (1996); Merzenich, M. M. et al., "Temporal processing deficits of language-learning impaired children ameliorated by training", Science, 271:77-81 (1996); Murphy, E., "Stroke rehabilitation", J. R. Coll. Physicians Lond., 33:466-468 (1999); Nagarajan, S. S. et al., "Speech modifications algorithms used for training language learning-impaired children", IEEE Trans. Rehabil. Eng., 6:257-268. (1998); Oddone, E. et al., "Quality Enhancement Research Initiative in stroke: prevention, treatment, and rehabilitation", Med. Care 38:192-1104 (2000); Rice-Oxley, M. and Turner-Stokes, L., "Effectiveness of brain injury rehabilitation", Clin. Rehabil., 13(Suppl 1):7-24 (1999); Tallal, P. et al., "Language learning impairments: integrating basic science, technology, and remediation", Exp. Brain Res., 123:210-219 (1998); Tallal, P. et al., "Language comprehension in language-learning impaired children improved with acoustically modified speech", Science, 271:81-84 (1996), which references are incorporated herein in their entirety by reference. ¶ 35.

Based on the cited art, it is clear that the level of skill in the art is high.

7. Working Examples

Examiner's Application: "The specification is limited to only two phosphodiesterase inhibitors, rolipram and iso-buto-metho-xanthine." OA, page 5.

Applicants' Response: See response above regarding Guidance of the Specification which is incorporated fully herein and which explains why the present

application should not be limited to the particular examples of phosphodiesterase inhibitors provided in the specification.

To demonstrate that the provided working examples sufficiently enable the claims as rejected (all phosphodiesterase inhibitors) and as amended (phosphodiesterase 4 inhibitors) Applicants submit the reference:

> MacDonald *et al.*, A Novel Phosphodiesterase Type 4 Inhibitor, HT-0712, Enhances Rehabilitation-Dependent Motor Recovery and Cortical Reorganization After Focal Cortical Ischemia, Neurorehabil. Neural Repair, OnlineFirst, published September 6, 2007 as doi: 10.1177/1545968307305521

This reference describes the beneficial effects of the phosphodiesterase 4 inhibitors, rolipram and HT0712 in the methods of the present invention. Particularly, this reference shows that:

> PDE4 inhibitors that modulate CREB function by enhancing cAMP signalling significantly enhance[s] functional recovery and cortical reorganization and after focal cortical ischemia. Administration of either rolipram or HT-0712 significantly enhance[s] motor recovery, and restoration/reorganization of residual motor maps in response to motor rehabilitation. Animals in both conditions had significantly larger residual motor maps than vehicle-injected animals.

MacDonald *et al.*, page 9. Applicants respectfully submit that this reference provides convincing evidence that "one skilled in the art would be able to make and use the claimed invention using the application as a guide." M.P.E.P. § 2164.05 (*citing In re Brandstadter*, 484 F.2d 1395, 1406-07, 179 USPQ 286, 294 (C.C.P.A. 1973)). Applicants also remind the Examiner that a party may properly rely on later publications to prove enablement of an earlier disclosure. *See, e.g., Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1335 (Fed. Cir. 2003) ("numerous post-filing publications demonstrated the extent of the enabling disclosure").

8. The Quantity of Experimentation Necessary

Examiner's Application: "The specification fails to provide support for all phosphodiesterase inhibitors. There is undue burden for experimentation with all phosphodiesterase inhibitors. Nor does it provide information to practice the claimed invention, absent undue experimentation." OA, page 5.

Applicants' Response: The test for enablement entails an analysis of whether one skilled in the art would have been able at the effective filing date to practice the

invention using the information disclosed in the application and information known in the art without undue or unreasonable experimentation. MPEP § 2164.01; *see In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). Applicants note that the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 13 (Fed. Cir. 1999). Moreover, even if experimentation may be difficult or time consuming, such experimentation is not necessarily "undue" in an art. *Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006), *cert. denied*, 127 S. Ct. 1151 (U.S. 2007). Here, Applicants acknowledge that experimentation could be necessary to determine if a particular compound acts as a phosphodiesterase inhibitor. However, given the relative skill of those in the art described above regarding (i) phosphodiesterase inhibition assays; and (2) methods to assess performance gains during treatment, Applicants respectfully submit that while experimentation could be necessary to practice the claimed invention, such experimentation would not be undue.

B. Claim Amendments

Based on the foregoing, Applicants respectfully submit that the present application fully enables the use of all phosphodiesterase inhibitors within the methods of the present invention. Nonetheless, and solely to expedite prosecution of the pending claim set, Applicants have restricted the claims to inhibitors of phosphodiesterase **4**.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the pending rejections of claims 1, 4-8, 14, 16-20, 49, 51-57, 60-64, 98 and 100-104 under 35 U.S.C. § 112.

II. Claim Rejections under 35 U.S.C. § 103

Claims 1, 4-8, 14, 16-20, 49, 51-57, 60-64, 98 and 100-104 stand rejected under 35 U.S.C. § 103 as allegedly obvious over United States Patent Number 5,547,979 (Christensen) in view of the Merck Manual. OA, page 7. According to the Examiner, "[t]he instant claims are directed to a method of increasing performance gain during treatment of a cognitive deficit associated with a central nervous system disorder by providing cognitive training and administering phosphodiesterase inhibitors." *Id.* The

Examiner argues that Christensen teaches the phosphodiesterase inhibitor rolipram in a method of treating stroke in a human. *Id.* The Examiner states that the limitations regarding "which enhances CREB pathway function" and "wherein rehabilitation of said cognitive deficit is effect by producing a long lasting performance gain" are given little patentable weight because these biological processes are inherent when the same compound is administered in the same patient population at the same dosage. *Id.*

Regarding the Merck Manual, the Examiner argues that it teaches that "a training protocol should be started as early as possible towards a patient's rehabilitation to stroke. Such rehabilitation includes encouragement, orientation toward the outside environment, eating, dressing, toilet functions, other basic needs, passive exercise, particularly of paralyzed limbs, and breathing exercises, if possible." *Id.* at 7-8. The Examiner concludes that these rehabilitation techniques meet the limitation of cognitive training. *Id.* at 8.

Based on these alleged teachings, the Examiner concludes that "it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have combined the cognitive multiple training sessions, as described in the Merck Manual, before and during administration of the phosphodiesterase inhibitor, rolipram, in the method of treating stroke in a human, as disclosed by Christensen." *Id.* The Examiner continues that a person of ordinary skill in the art would have been motivated to combine the two allegedly disclosed methods of treating a stroke patient because (1) both Christensen and the Merck Manual disclose treatment for the same purpose, which is treating stroke patients and because (2) of the additive therapeutic effects of employing two methods of treating stroke simultaneously. *Id.* Applicants respectfully traverse.

To maintain a proper rejection under 35 U.S.C. § 103, the Examiner must meet four conditions to establish a *prima facie* case of obviousness. First, the Examiner must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Examiner must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an

obviousness rejection is based on some combination of prior art references, the Examiner must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak,* 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Following *KSR Int'l Co. v. Teleflex, Inc.*, this fourth prong of the prima facie obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966). 550 U.S. __ (2007); 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966).

The present amendments to the claims add the language "repeating said providing and said administering of steps (a) and (b) until a long-lasting performance gain relative to the performance of said cognitive task achieved by training alone is produced." Christensen relates to the treatment of a stroke episode by administering an effective "TNF inhibiting amount" of a compound. Regarding stroke particularly, Christensen relates to the idea that TNF has pro-inflammatory activities, which "together with its *early* production (during the *initial* stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including... stroke." Christensen, Col. 6, ll. 20-26 (emphasis added). Thus, Christensen relates to the administration of rolipram during the initial *acute* phase of a stroke episode to treat *acute* tissue injury. Christensen does not teach or suggest that the compounds are phosphodiesterase inhibitors. Christensen also does not teach or suggest the administration of the compounds after the acute phase of the inflammatory event has ended. Christensen does not teach administering the compounds during training or that one could achieve a performance gain during training by the administration of phosphodiesterase inhibitors before or during training.

The Merck Manual relates to training protocols it allegedly asserts should be started as early as possible towards a patient's rehabilitation following stroke. The Merck Manual does not teach or suggest the administration of phosphodiesterase inhibitors before or during training. The Merck Manual also does not teach or suggest that one could achieve a performance gain during training by the administration of phosphodiesterase inhibitors before or during training. Neither Christensen nor the

Merck Manual, either alone or in combination, provides any teaching or suggestion of a beneficial link between the inhibition of phosphodiesterases and cognitive training and the present rejection must therefore be reconsidered and withdrawn for this reason alone.

Moreover, the Examiner appears to rely on an inherency theory to support the outstanding rejections. The Examiner appears to reason that if rolipram therapy is administered immediately following stroke and cognitive therapy is begun as early as possible following stroke, a performance gain would necessarily result. This is nothing more than hindsight reconstruction. *See In re McLaughlin*, 443 F.2d 1392 (C.C.P.A. 1971).

Supporting the stated interpretation of the Examiner's position, Applicants note that the Examiner states that the limitations regarding "which enhances CREB pathway function" and "wherein rehabilitation of said cognitive deficit is effect by producing a long lasting performance gain" are given little patentable weight because these biological processes *are inherent* when the same compound is administered in the same patient population at the same dosage. OA, page 7.

First, Applicants point out that "inherency may not be established by probabilities or possibilities." *Ex Parte Skinner*, 2 U.S.P.Q.2d 1788 (B.P.A.I. 1986). Critically, the Examiner has provided no evidence that the administration timeline contemplated by Christensen overlaps with that described by the Merck Manual. That is, it is only a *possibility* that the "as early as possible" timeline described in the Merck Manual would overlap with the acute inflammation reduction following stroke in Christensen.

Second, inherency cannot be used to support a rejection under 35 U.S.C. § 103 because "[t]hat which may be inherent is not necessarily known" and "[o]bviousness cannot be predicated on what is unknown." *Application of Shetty*, 566 F.2d 81 (C.C.P.A. 1977); *see also In re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993). Moreover, the view that success would have been 'inherent' cannot substitute for a showing of reasonable expectation of success." *Application of Rinehart*, 531 F.2d 1048 (C.C.P.A. 1976). Thus, to the extent the Examiner relies on a theory of inherency to support the outstanding 35 U.S.C. § 103, such reliance is improper.

Nonetheless, and solely to expedite prosecution of the pending claim set, the pending claims have been amended to state that the providing and administering steps

of the claims are **repeated until** a long-lasting performance gain relative to the performance of said cognitive task achieved by training alone is produced. Because neither Christensen nor the Merck Manual, nor Christensen and the Merck Manual in combination, understood any connection between administering a phosphodiesterase inhibitor and cognitive training, these references, either alone or in combination do not disclose **repeating** said providing **and** said administering of steps (a) and (b) **until** a long-lasting performance gain relative to the performance of said cognitive task achieved by training alone is produced. Therefore, these references, singly or in combination, do not teach or suggest all of the claim limitations. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991)

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejections of claims 1, 4-8, 14, 16-20, 49, 51-57, 60-64, 98 and 100-104 stand rejected under 35 U.S.C. § 103 as allegedly obvious over United States Patent Number 5,547,979 (Christensen) in view of the Merck Manual.

CONCLUSION

Applicants have properly and fully addressed each of the Examiner's grounds for rejection. Applicants submit that the present application is now in condition for allowance. If the Examiner has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited. If there are any additional fees due in connection with the filing of this amendment, please charge the fees to undersigned's Deposit Account No. 50-1067. If any extensions or fees are not accounted for, such extension is requested and the associated fee should be charged to our deposit account

Respectfully submitted,

Date: 06 May 2008

Don J. Pelto
Reg. No. 33,754

Sheppard Mullin Richter & Hampton LLP
1300 I Street NW
Eleventh Floor East
Washington, D.C. 20005
Tel: (202) 772-5362
Fax: (202) 312-9415